Modulation of the Immune Response in Breast Cancer: Dream or reality?

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Evidence for Immunity in Cancer

• Spontaneous tumor regressions (melanoma and lymphoma)

• Higher incidence of tumors in immunosuppressed, immunodeficient (AIDS) as well as older patients

• Regression of metastases after removal of primary tumor (renal cell ca)

• Lymphocyte infiltration of tumors and associations with prognosis
Cancer immunoediting—elimination, equilibrium and escape

Schreiber and Smyth Science 2011
Cancer Immunoeediting

Transformed cells

- "Danger" signals
- Tumor antigens
- NK ligands

Intrinsic tumor suppression (senescence, repair, and/or apoptosis)

Caricinogens
Radiation
Viral infections
Chronic inflammation
Inherited genetic mutations

Normal tissue

Elimination

- CD8+ T cell
- CD4+ T cell
- NKT cell
- NK cell

Equilibrium

- IFN-γ
- IFN-α/β
- IL-12
- TNF
- NKG2D
- TRAIL
- Perforin

Tumor dormancy and editing

Escape

- IL-6, IL-10
- Galectin-1
- TGF-β
- IDO
- PD-L1

Antigen loss
MHC loss

Tumor growth promotion

Extrinsic tumor suppression

Normal cell

Highly immunogenic
transformed cell

Poorly immunogenic
and immunoavasive
transformed cells

Innate & adaptive immunity

Schreiber and Smyth Science 2011
What’s happening in breast cancer?

- Tumor infiltrating lymphocytes (TILs) are seen in primary breast cancer.

- Associated with a better prognosis in primary TNBC treated with anthracycline-based chemo.

- Associated with a better prognosis in primary HER2+ BC treated with anti-HER2 therapy+chemo.
Higher levels in HER2+ and TNBC

Loi et al, JCO 2012; Ann Oncol 2014
### Primary TNBC post adjuvant CT

**Table 1.** Recently Published Data on the Prognostic Value of TILs in Primary TNBC

<table>
<thead>
<tr>
<th>Dataset</th>
<th>BIG 2-98</th>
<th>FinHER</th>
<th>ECOG 2197 and ECOG 1199</th>
<th>Post Neoadjuvant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical trial dataset</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes*</td>
<td>No</td>
</tr>
<tr>
<td>TILs evaluated before (at diagnosis) or after chemotherapy</td>
<td>Before</td>
<td>Before</td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>No. of patients with TNBC</td>
<td>256</td>
<td>145</td>
<td>481</td>
<td>278</td>
</tr>
<tr>
<td>Node positive, %</td>
<td>100</td>
<td>78.5</td>
<td>59</td>
<td>54</td>
</tr>
<tr>
<td>Median follow-up, years</td>
<td>8</td>
<td>5.2</td>
<td>10.6</td>
<td>6.3</td>
</tr>
<tr>
<td>Chemotherapy type</td>
<td>Anthracycline/taxane</td>
<td>Anthracycline/taxane/ vinorelbine</td>
<td>Anthracycline/taxane</td>
<td>Anthracycline/taxane</td>
</tr>
<tr>
<td>Median %</td>
<td>20</td>
<td>25</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>IQR, %</td>
<td>12.5-30</td>
<td>12.5-40</td>
<td>10-20</td>
<td>10-30</td>
</tr>
<tr>
<td>Significant association with involved axillary LNs at diagnosis</td>
<td>No</td>
<td>Yes: more TILs, more LN+</td>
<td>Yes: more TILs, more LN+</td>
<td>NA</td>
</tr>
<tr>
<td>LPBC, %†</td>
<td>10.6</td>
<td>11.6</td>
<td>4.4</td>
<td>14.8</td>
</tr>
<tr>
<td>Stromal TILs (10%) HR (adjusted)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DFS</td>
<td>0.85</td>
<td>0.82</td>
<td>0.84</td>
<td>NG</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.74 to 0.98</td>
<td>0.67 to 0.99</td>
<td>0.74 to 0.95</td>
<td></td>
</tr>
<tr>
<td>*P</td>
<td>0.025</td>
<td>0.047†</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>DDFS</td>
<td>NG</td>
<td>0.77</td>
<td>0.81</td>
<td>0.86</td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td>0.61 to 0.98</td>
<td>0.68 to 0.97</td>
<td>0.77 to 0.96</td>
</tr>
<tr>
<td>*P</td>
<td></td>
<td>0.02</td>
<td>0.02</td>
<td>0.01</td>
</tr>
<tr>
<td>OS</td>
<td>0.83</td>
<td>0.81</td>
<td>0.79</td>
<td>0.86</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.71 to 0.98</td>
<td>0.61 to 1.1</td>
<td>0.67 to 0.92</td>
<td>0.77 to 0.97</td>
</tr>
<tr>
<td>*P</td>
<td>0.023</td>
<td>.1</td>
<td>.003</td>
<td>.01</td>
</tr>
</tbody>
</table>

Loi et al, JCO 2014
What do TILs represent?

• TILs represent pre-existing host anti-tumor immunity
  – The more the better

• An activated immune response which has been terminated (naturally) or attenuated (tumor-mediated).
FOR TNBC AND HER2+ BC, IMMUNE APPROACHES MAY BE ABLE TO IMPROVE DISEASE OUTCOMES.
Questions going forward in developing immune approaches in BC

• Why do some patients have TILs in their tumor: pre-existing immunity?

• How can we enhance the immune response or create an immune response where none exists?

• Will TILs be a biomarker of response to T cell checkpoint inhibition (or other immunotherapies) or will we need PDL1+?

• Will T cell checkpoint inhibition be enough?
Mutations act as tumor antigens

Lawrence et al, Nature 2013
Immunogenic mutations in breast cancer

• The spectrum of “immunogenic” peptides is yet to be described.

• TNBC have higher mutational load= higher TILs

• HER2+ also higher mutational load as well as overexpression of HER2 protein.

• BRCA1-mutated tumors classically associated with high TILs
NEGATIVE REGULATION OF IMMUNITY

Chen and Mellman, Immunity 2012
Radiotherapy Increases the Permissiveness of Established Mammary Tumors to Rejection by Immunomodulatory Antibodies

Inge Verbrugge, Jim Hagekyriakou, Leslie L. Sharp, et al.
BOSTON trial I/II

• Pilot study of Stereotactic ablative radiotherapy (SABR) +/- anti-PD1- antibody
• Objective to assess safety and immune endpoints
• Population is oligo-metastatic breast cancer (1-3 mets).
Augmenting T cell responses with trastuzumab

Background BALB/c MMTV/neu mice

Stagg et al, PNAS 2011
PANACEA trial: NCT02129556

Phase Ib/II trial of anti-PD-1 monoclonal ANtibody in AdvanCed, Trastuzumab-resistant, HER2-positive breast cAncer

Advanced HER2+ BC
Trastuzumab resistant
Up to 3 lines previous anti-HER2 therapy

Confirmed PD-L1 expression on metastatic lesion

Tratuzumab+MK3475 until progression
Biopsy on PD

Primary Endpoint is efficacy of the combination
Will TILs be a biomarker of response to T-cell checkpoint inhibition?

- Correlation between TILs and T cell checkpoints.
- TILs per se may overcome issues of IHC (see guidelines paper by Salgado et al, Annals of Oncology).
- Pre-existing immunity is important.

Savas et al 2014
Other possibilities to enhance immunity

• Will one immunotherapy be enough?
  – Blockade of additional checkpoints: PD1, PDL1, TIM-3, LAG3, VISTA etc (lots of T negative regulators)
  – Adenosine, IDO-1, ICOS, other immunosuppressive molecules
  – OX40, 41BB

• Standard BC therapies
  – Chemotherapies- gemcitabine, cisplatin
  – Targeted therapies- priming and cell death
  – Radiation
Conclusions for immune modulation in breast cancer

• There is correlative and preclinical data suggesting that immunotherapies will be effective for certain subtypes of BC
  – Await clinical trials

• Pre-existing immunity is present in some patients
  – Relief of negative regulation seems to be most important
  – TILs *per se* likely an appropriate biomarker for T cell checkpoint inhibition

• Will T cell checkpoint inhibition be enough?
  – Many std therapies likely synergistic.
  – Combinations of IT likely
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